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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/648,636	08/26/2003	Vijay Kumar Handa	2003-016	3904

7590 08/29/2005

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EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 08/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/648,636	HANDA ET AL.	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,2,7,8 and 13* is/are allowed.

6)☒ Claim(s) *3-6 and 9-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-6 and 9-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 refers to a "methylated compound of Formula II." It is not entirely clear whether this recitation is intended to refer to a Formula II compound which bears an *additional* methyl group somewhere on the molecule, as would be its literal meaning, or if it merely refers to "the compound of Formula II," which is *formed by* methylation of another compound. Since claim 4 depends from claim 3, claim 4 is indefinite as well.

In independent claims 5, 7, 9, 11 and 12 multiple references are made to compounds of Formulae VII, VIII, II and VII. An independent claim may not refer to another independent claim for definitions of variables, nor refer to a formula of a specific number, without providing a definition for that formula.

Claims 6, 8 and 10, which depend from claims 5, 7 and 9 respectively, are indefinite because those claims depend from indefinite base claims.

Claim 12 is further indefinite for the reason that it does not end with a period, implying that there is more to the claim than is shown.

DETAILED ACTION

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The following is a quotation of the second paragraph of 35 U.S.C. 112:

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In independent claims 5, 7, 9, 11 and 12 multiple references are made to compounds of Formulae VII, VIII, II and VII. An independent claim may not refer to another independent claim for definitions of variables, nor refer to a formula of a specific number, without providing a definition for that formula.

Claims 6, 8 and 10, which depend from claims 5, 7 and 9 respectively, are indefinite because those claims depend from indefinite base claims.

Claim 12 is further indefinite for the reason that it does not end with a period, implying that there is more to the claim than is shown.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 5 and 6 are rejected under 35 U.S.C. 102(a) and 35 U.S.C. 102(e) as being anticipated by WO 02/090339 (Rao et al), based on the international filing date of that publication, which date is 6 May 2002, and on the publication date of 14 November 2002. Rao et al designates the United States and is in the English language, so it qualifies as 102(e) art.

The process according to instant claims 5 and 6 is disclosed on page 2, steps (i)-(iv), and page 3, starting at line 24, to page 4, lines 1-12.

The compound 1-benzyl-4-methyl-2-phenylpiperazine, compound of Formula VII, as obtained in instant claim 3, is hydrogenated with Pd-C to 1-methyl-3-phenylpiperazine, the compound of formula I as specified in instant claim 5.

The product-by-process limitation in claim 5 does not require the starting material, the compound of Formula VII, to have been obtained according to the process of claim 3, only that it be the compound of Formula VII, which is what the starting material in the reaction cited in the Rao et al publication is.

Allowable Subject Matter

Claims 1, 2, 7, 8 and 13 are allowed.

Claims 3, 4 and 9-12 would be allowable if rewritten or amended to overcome the rejections under 35 U.S.C. 112, second paragraph, set forth in this Office action.

Claims 5 and 6 should be cancelled.

The process according to the instant claims, and the compound according to claim 13 are novel and unobvious. Close prior art is summarized in the following paragraphs:

Also, although not the basis for any rejection, the language of claim 8, in the opinion of the examiner, is awkward. Instead of reciting "where the hydrogenating step is *done* in acetic acid," the language of claim 12 should be changed to "where the hydrogenating step is *conducted* in acetic acid."

Many prior art methods for making the compound made by the instantly claimed process are known from the prior art (1-methyl-3-phenylpiperazine).

Page 1 of the specification cites the best known, which was first reported by Roderick et al, *Journal of Medicinal Chemistry*, vol. 9(2), pages 181-185 (1965). Roderick et al's process does not involve a benzyl-protected intermediate, as does the instantly claimed process.

US 4,772,705 (Schmiesing) teaches a process which entails reduction of 2-phenylpiperazin-2-one, and *then* methylating the product with methyl iodide in the presence of triethylamine (example 4 of the patent). Schmiesing proceeds in reverse fashion to instant claim 9. Schmiesing does not suggest reversing the steps, and

instead starting with an N-methylated phenylpiperazinone precursor. To do so in the absence of an express suggestion would not have been *prima facie* obvious to one of ordinary skill, because the basic reagents needed to methylate an amido-nitrogen, as in the 1-methyl-3-phenyl-piperazine-2-one starting material needed for such a process, are much stronger than the triethylamine employed by Schmiesing in this step. The instant specification employs sodium hydride for methylating 3-phenylpiperazin-2-one. Sodium hydride is not obvious over triethylamine, especially since Schmiesing does not mention this reagent anywhere in his patent, and also because it is several orders of magnitude stronger in its basicity (hydride ion *versus* an organic amine).

Ikeda et al, "Piperazine Compounds. VI. Antihistaminic and Anticholinergic Effects of 2-Phenylpiperazine Derivatives" Yakugaku Zasshi, vol. 90(11), pages 1452-1456 (1970) teaches still another process for making the product of the process of the instant claims (see compound "**3**" on the first page of the reference). Ikeda et al disclose a synthesis of antihistamine drugs. The reference is in Japanese, but since the benzylated phenylpiperazinone intermediate is not disclosed in Ikeda et al, by inference, one can conclude that the process of the instant claims is not taught in that reference.

Another alternate method of making 1-methyl-3-phenyl-piperazine is CA 2 370 389 (Dolitzky). This Canadian patent application publication makes known a process whereby 1-alkyl-3-phenyl-piperazine-2 is made by cyclization of the appropriate alkyl-(2-haloethyl)-[(2-halo-2-phenyl)ethyl]amine in a reaction with tosylamide (pages 3-5).

According to Dolitzky, the product, a 4-tosylated piperazine compound, is hydrolyzed to remove the tosyl group, affording the 1-methyl-3-phenyl-piperazine.

Guo et al, "An Efficient Process for Preparing 4-Methyl-2-phenyl Piperazine Hydrochloride and its Derivatives" Chinese Chemical Letters, vol. 14(4), pages 365-367 (2003), discloses a similar process to the instantly claimed process. The starting material is different than is used in the process of the invention. A benzyl-protected intermediate is part of the Guo et al process, but the sequence of reduction of the keto group and methylation of the piperazine nitrogen are reversed, with no suggestion or mention of inverting these two steps provided in the reference. One of ordinary skill would not be motivated to methylate the benzyl-protected piperazinone intermediate *and then* reduce the keto function, as is the case in the instant claims, in the absence of any suggestion to do so, especially since no advantage would be expected in doing so.

Lastly cited as an alternate method for making the products of the claimed process is CA 2 4690 571 (Llado et al). Llado et al's process is more involved than the other syntheses described *supra*, but has the advantage of avoiding methylation of the unwanted nitrogen atom, like the instantly claimed process does. Formation of a phenyl-substituted diketo piperazine by cyclization of a N-acetyl-D,L-phenylglycine-N'-methylamide compound, followed by reduction of the keto groups is essentially the idea of the process taught by Llado et al (pages 5 and 6).

The compound of instant claim 13, which compound is an intermediate in the novel process of the invention, is novel over the prior art. Close prior art to the compound of claim 13 comes from Haberl, R. "Über die Herstellung C-methyl-phenyl-

substituierter Piperazine" Monatshefte für Chemie, vol. 89(6), pages 798-805 (1958). At page 804, the compund 1,2-dimethyl-3-phenyl-4-benzylpiperazine is disclosed. If it were not for the 2-methyl group, which is a keto function in the compound of claim 13,, this would be the compound of claim 13.

Conclusion

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Tuesday-Thursday from 8:00am to 4:30pm or Monday from 6:00am to 1:30pm. If Attempts to reach the examiner are unsuccessful, contact the examiner's supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

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